

Remarks

I. Support for the Amendments

Support for the foregoing amendments to the claims may be found throughout the specification, and in the original claims. No new matter was added by way of this amendment.

II. Status of the Claims

By the foregoing amendments, claims 1-32 have been canceled, and claims 33-103 have been added. Upon entry of the foregoing amendments claims 33-103 are pending in the present application, with claims 33, 47, 64, 79, and 92 being the independent claims.

III. Summary of the Office Action

In the Office Action dated September 7, 2000, the Examiner has made twelve rejections to the claims. Applicants respectfully offer the following remarks to overcome or traverse each of the elements of the Office Action.

IV. The Rejection of Claim 29, Under 35 U.S.C. § 112, First Paragraph is Traversed.

In the Office Action at page 2, the Examiner has rejected claim 29 under 35 U.S.C. § 112, first paragraph, because the specification does not provide enablement of any composition for making an increased amount or percentage of full-length cDNA. Applicants respectfully traverse this rejection.

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It is apparent from the comments made by the Examiner that the rejection actually was intended to relate to the composition of claim 30 rather than the kit of claim 29. However, for reasons other than patentability claim 30 was canceled by the foregoing amendments. Hence, the examiner's rejection is rendered moot. Reconsideration and withdrawal are respectfully requested.

V. The Rejection of Claim 5, Under 35 U.S.C. § 112, Second Paragraph is Traversed.

In the Office Action at page 3, the Examiner has rejected claim 5 under 35 U.S.C. § 112, second paragraph for containing indefinite language. Applicants respectfully traverse this rejection.

For reasons other than patentability, claim 5 has been canceled by the foregoing amendments. Hence, the examiner's rejection is rendered moot. Reconsideration and withdrawal are respectfully requested.

VI. The Rejection of Claim 7, Under 35 U.S.C. § 112, Second Paragraph is Traversed.

In the Office Action at page 3, the Examiner has rejected claim 7 under 35 U.S.C. § 112, second paragraph for containing indefinite language. Applicants respectfully traverse this rejection.

For reasons other than patentability, claim 7 has been canceled by the foregoing amendments. Hence, the examiner's rejection is rendered moot. Reconsideration and withdrawal are respectfully requested.

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VII. The Rejection of Claim 13, Under 35 U.S.C. § 112, Second Paragraph is Traversed.

In the Office Action at pages 3 and 4, the Examiner has rejected claim 13 under 35 U.S.C. § 112, second paragraph for containing indefinite language. Applicants respectfully traverse this rejection.

For reasons other than patentability, claim 13 has been canceled by the foregoing amendments. Hence, the examiner's rejection is rendered moot. Reconsideration and withdrawal are respectfully requested.

VIII. The Rejection of Claim 16, Under 35 U.S.C. § 112, Second Paragraph is Traversed.

In the Office Action at page 4, the Examiner has rejected claim 16 under 35 U.S.C. § 112, second paragraph for containing indefinite language. Applicants respectfully traverse this rejection.

For reasons other than patentability, claim 16 has been canceled by the foregoing amendments. Hence, the examiner's rejection is rendered moot. Reconsideration and withdrawal are respectfully requested.

IX. The Rejection of Claims 29 and 30, Under 35 U.S.C. § 112, Second Paragraph is Traversed.

In the Office Action at page 4, the Examiner has rejected claims 29 and 30 under 35 U.S.C. § 112, second paragraph for containing indefinite language. Applicants respectfully traverse this rejection.

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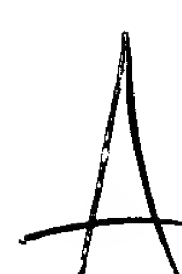
For reasons other than patentability, claims 29 and 30 has been canceled by the foregoing amendments. Hence, the examiner's rejection is rendered moot. Reconsideration and withdrawal are respectfully requested.

X. *The Rejection of Claims 18 and 19, Under 35 U.S.C. § 112, Second Paragraph is Traversed.*

In the Office Action at page 4, the Examiner has rejected claims 18 and 19 under 35 U.S.C. § 112, second paragraph for containing indefinite language. Applicants respectfully traverse this rejection.

For reasons other than patentability, claims 18 and 19 have been canceled by the foregoing amendments. However, the rejection as it may relate to the new claims is traversed.

In the Office Action, at page 4, the Examiner requests clarification and asks, "... if the mRNA of claim 18 is single stranded, how is it possible that it is in the mRNA/cDNA hybrid?" When a cDNA molecule is synthesized from an mRNA template, either a full length or truncated cDNA strand can result. When a full-length cDNA molecule is synthesized, a completely double stranded cDNA/mRNA hybrid molecule will result. When a truncated cDNA molecule is synthesized the remaining bases of the mRNA template that are not reverse transcribed extend from the cDNA/mRNA hybrid molecule as a single stranded mRNA molecule. According to one aspect of the invention, this single stranded mRNA is digested with a ribonuclease, while the mRNA contained in the double stranded cDNA/mRNA hybrid is not digested. Additionally, many mRNA molecules contain a cap structure attached to the 5'-terminal base; therefore, if single stranded mRNA is present and digested, the cap structure



will be removed. Meanwhile, the cap structures of the cDNA/mRNA hybrid molecules with full length cDNA strands will remain attached to the mRNA template. The presence of this cap structure can then be used as a selection criteria for full length cDNA molecules. New claims 64-78 are directed to these embodiments.

In view of the foregoing amendments and remarks, Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

XI. The Rejection of Claims 1-6, 15-16, and 21-30 Under 35 U.S.C. § 102(b) is Traversed.

In the Office Action at page 5, the Examiner has rejected claims 1-6, 15-16, and 21-30 under 35 U.S.C. § 102(b) as being anticipated by Sloma (U.S. Pat. No. 4,748,233). Applicants respectfully traverse this rejection.

For reasons other than patentability claims 1-6, 15-16 and 21-30 have been cancelled by the foregoing amendments. However, the rejection as it may relate to the new claims is respectfully traversed.

Sloma teaches a method for producing cDNA, wherein the "solution is incubated at an elevated temperature, e.g., about 40-50°C., for a time sufficient to allow formation of the cDNA copy" (Column 4, lines 35-37). This passage suggests that Sloma uses this elevated temperature during the DNA synthesis reaction, where the cDNA strand is being synthesized by the reverse transcriptase, and not during the annealing phase of the reaction. Further, Sloma teaches synthesis of a complementary cDNA strand "under essentially the same conditions as the synthesis of the cDNA copy" (Column 4, lines 57-59).

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The present invention is directed to methods for synthesizing one or more cDNA molecules or a population of cDNA molecules at temperatures that inhibit, prevent, reduce or substantially reduce internal priming. Sloma does not teach or suggest the use of elevated temperatures to decrease internal priming; rather Sloma teaches the use of elevated temperatures during the synthesis phase of the reaction.

Further, the present invention is also directed to methods for producing double stranded cDNA under conditions that improve the percentage of full length double stranded cDNA. These methods include optimizing the ribonuclease digestion conditions. Sloma does not teach any methods for optimizing the percent yield of double stranded cDNA produced over conventional techniques. Moreover, Sloma does not teach or suggest the optimization of ribonuclease digestion conditions to improve the percentage of double stranded cDNA.

In view of the foregoing amendments and remarks, Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

XII. The Rejection of Claims 7 and 8 Under 35 U.S.C. § 103(a) is respectfully traversed.

In the Office Action at pages 7 and 8, the Examiner has rejected claims 7 and 8 under 35 U.S.C. § 103(a) as being unpatentable over Sloma, in view of Copeland *et al.* (U.S. Pat. No. 6,103,473). Applicants respectfully traverse this rejection.

For reasons other than patentability, claims 7 and 8 were canceled in the foregoing amendments. Therefore, the rejection as it relates to the canceled claims has been rendered moot. This rejection, as it may relate to any of the new claims is respectfully traversed.

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Claims 40-42 relate to methods for producing cDNA under conditions that inhibit, prevent, reduce or substantially reduce internal priming. Specifically, these conditions comprise the use of primer to template ratios lower than those of conventional methods.

Sloma teaches a method of producing cDNA from an mRNA template using AMV reverse transcriptase and a poly-dT primer, at an elongation temperature of 40-50 degrees C. Copeland teaches a method for producing DNA from a DNA template using a primer to template ratio of 1:1.

In rejecting a claim under 35 U.S.C. § 103(a) the Examiner bears the burden of establishing a *prima facie* case of obviousness. In order to do so there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine referenced teachings to obtain the claimed invention, *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). As the Federal Circuit has held numerous times, a hindsight analysis such as that employed by the Examiner in the present case is impermissible; instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985).

Neither Sloma nor Copeland *et al.* teach or suggest the use of a low primer to template ratio in preparing cDNA. Moreover, they do not teach or suggest the use of lower primer to template ratios to decrease the amount of internal priming. (See Example 1 of the present application). As such, the Examiner has not met the burden required to sustain a *prima facie* case of obviousness.

In view of the foregoing amendments and remarks, Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

XIII. The Rejection of Claims 9-11 Under 35 U.S.C. § 103(a) is Traversed.

In the Office Action at pages 8 and 9, the Examiner has rejected claims 9-11 as being unpatentable over Sloma, in view of Scalice *et al.* (U.S. Pat. No. 5,587,287) and Odawara *et al.* (U.S. Pat. No. 5,989,819). Applicants respectfully traverse this rejection.

For reasons other than patentability claims 9-11 were canceled in the foregoing amendments. Therefore, the rejection as it relates to the canceled claims has been rendered moot. This rejection, as it may relate to any of the new claims, is respectfully traversed.

Claims 49-51 of the present invention relate to a method for synthesizing cDNA molecules, or a population of cDNA molecules comprising mixing at least one mRNA template, poly A mRNA template or population of such templates, with at least one polypeptide having reverse transcriptase activity and an inhibitor of the polypeptide having reverse transcriptase activity, under conditions that inhibit, prevent, reduce or substantially reduce the synthesis of non-specific cDNA products when compared to when the inhibitor is absent. One example of such an inhibitor is an antibody.

The teachings of Sloma are described previously. Scalice *et al.* teach the use of anti-DNA polymerase antibodies for use in PCR methods, to reduce the formation of non-specific products in these reactions. Odawara *et al.* teach an antibody having the ability to inhibit the activity of a reverse transcriptase derived from HIV. Such antibodies are used in methods to

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characterize the HIV virus, e.g. HIV having acquired drug resistance, and to determine changes in an infected host which occur during the progression of the illness.

As was discussed previously, in rejecting a claim under 35 U.S.C. § 103(a) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine referenced teachings to obtain the claimed invention, *See In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). It is not enough that the combination of the cited references would have been obvious to try. Neither Sloma, Scalice *et al.*, nor Odawara *et al.* teach or suggest the use of an antibody to reverse transcriptase in cDNA synthesis reactions. While Scalice *et al.* do teach a method for reducing non-specific PCR products using an anti-DNA polymerase antibody, they do not suggest the use of this method for the synthesis of cDNA. Likewise, Odawara *et al.* teach a method of quantitatively determining the ability of an anti-reverse transcriptase antibody to inhibit reverse transcriptase activity. However, Odawara *et al.* do not teach or suggest the use of this antibody in a method to reduce the synthesis of non-specific cDNA products. Instead, the teachings of Odawara *et al.* are directed to use of such antibodies in characterizing HIV infection. Thus, the teachings of Odawara *et al.* are in a non-analogous art and are not properly combinable with Sloma and Scalice *et al.* Moreover, Odawara *et al.* teach that the addition of an anti-reverse transcriptase antibody completely inhibits reverse transcriptase activity, and therefore teaches away from the present invention.

In view of the foregoing amendments and remarks, Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

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XIV. The Rejection of Claims 12-14, Under 35 U.S.C. § 103(a) is Traversed.

In the Office Action at pages 9-10, the Examiner has rejected claims 12-14 as being unpatentable over Sloma in view of Ranu (U.S. Pat. No. 5,824,875). Applicants respectfully traverse this rejection.

For reasons other than patentability claims 12-14 were canceled in the foregoing amendments. Therefore, the rejection as it relates to the canceled claims has been rendered moot. This rejection, as it may relate to any of the new claims, is respectfully traversed.

Claims 43-46 relate to a method for synthesizing one or more cDNA molecules or a population of cDNA molecules comprising, mixing at least one mRNA template, poly A RNA template or population of such templates with at least one polypeptide having reverse transcriptase activity, under conditions that inhibit, prevent, reduce or substantially reduce internal priming. These conditions include the use of a primer having a relatively long length.

The teachings of Sloma have been described previously. Ranu teaches the use of a 50-mer primer to be used as an anti-sense inhibitor of ACC synthase gene expression. Ranu does not teach or suggest a method of using a long primer in cDNA synthesis. Rather Ranu teaches a method by which a primer of 6-100 nucleotides can be used for the "specific alteration, primarily inhibition, of ACC synthase gene expression in cells." (Column 15, lines 18-20). Further, Ranu teaches that the oligonucleotides "may extend in length up to and beyond the full coding sequence for which it is antisense." (Column 15, lines 13-14). The use of such an oligonucleotide extending beyond the full coding sequence in the methods of the present invention would result in no cDNA synthesis because there would be no remaining template for the reverse transcriptase to utilize. Thus, not only is there no suggestion or motivation for

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one of ordinary skill in the art to use the antisense nucleotide of Ranu with the invention of Sloma, but if the two references were combined they would not result in the present invention. As such, there would be no reasonable expectation of success even if the references were combined. Therefore, the Examiner has failed to prove a *prima facie* case of obviousness.

In view of the foregoing amendments and remarks, Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

XV. The Rejection of Claims 17-20 Under 25 U.S.C. 103(a), is Traversed.

In the Office Action at pages 10-11, the Examiner has rejected claims 17-20 as being unpatentable over Sloma, in view of Vlatsuk *et al.* (U.S. Pat. No. 6,096,877). Applicants respectfully traverse this rejection.

For reasons other than patentability claims 17-20 were canceled in the foregoing amendments. Therefore, the rejection as it relates to the canceled claims has been rendered moot. This rejection, as it may relate to any of the new claims, is respectfully traversed.

Claims 64-77 of the present invention relate to a method for producing full length cDNA, comprising incubating at least one mRNA template, poly A RNA template or population of such templates with at least one peptide having reverse transcriptase activity under conditions to make one or more nucleic acid molecules complementary to all or a portion of the template to give mRNA/cDNA hybrids, digesting said mRNA/cDNA hybrids under conditions which cleave the cap structure of hybrid mRNA/cDNA that does not contain full length cDNA, and selecting for said full length cDNA hybrids. The digestion is preferably a ribonuclease digestion.

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When a cDNA molecule is synthesized from an mRNA template either a full length cDNA molecule or a truncated cDNA molecule can be produced. When a truncated cDNA molecule is produced, the 5' bases of the mRNA template that were not reverse transcribed extend from the double stranded cDNA/mRNA hybrid molecule as an unhybridized, single stranded mRNA molecule. In accordance with this embodiment of the invention, the conditions for ribonuclease digestion are optimized so that these single stranded mRNA extensions are digested, while the hybridized mRNA strand (contained in the cDNA/mRNA hybrid molecule) remains undigested. When the single stranded mRNA extension is cleaved the cap structure is also cleaved, leaving the cDNA/mRNA hybrid molecule without a cap structure. On the other hand, if a full length cDNA molecule is produced, then there is no single stranded mRNA present, and therefore there is no significant ribonuclease cleavage. Therefore, the cap structure remains attached to the 5'-terminal mRNA base.

The presence of this cap structure can then be used as a criteria for selection of full length cDNA molecules, since the only mRNA molecules containing cap structures will be those from which a full length cDNA was reverse-transcribed. This selection can be carried out using a cap structure binding molecule such as eIF4E, eIF4E peptides, eIF4E peptide fragments, and anti-cap structure antibodies.

Vlasuk *et al.* teach a method for degrading the entire mRNA strand in a cDNA/mRNA hybrid molecule, and creating a double stranded cDNA molecule by synthesizing the second cDNA strand. Vlasuk *et al.* do not teach or suggest digesting the mRNA/cDNA hybrid molecules under conditions which cleave the cap structure of the hybrid mRNA/cDNA that does not contain full length cDNA. Further, they do not teach or suggest the use of the

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ribonuclease digestion in methods to select full length mRNA/cDNA hybrids. Moreover, if the conditions of Vlasuk *et al.* were used in the present invention, they would result in the complete digestion of the mRNA strand and thus the removal of the cap structure, resulting in the inability to select for full length cDNA molecules. Therefore, not only is there no suggestion or motivation for one skilled in the art to combine the teachings of Sloma and Vlasuk *et al.*, but the cited references teach away from, and if combined would not result in, the present invention. As such, a person skilled in the art would have no motivation to combine the cited references, and if they were combined there would be no reasonable expectation for success.

In view of the foregoing amendments and remarks, Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

XVI. Summary

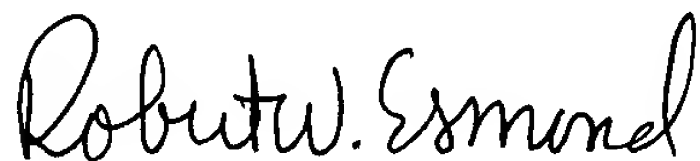
All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

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Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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